

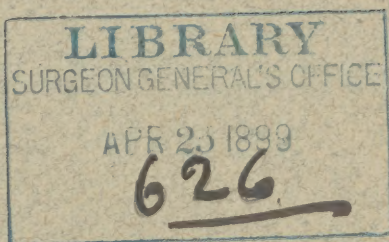
Fütterer (G.)

**The Elimination of Bacteria from the General Circulation
by the Liver and through the Bile Passages.**

**A Claim for Priority in Stating the Presence of the Bac-
illus Typhi Abdominalis in the Gall-Bladder.**

BY

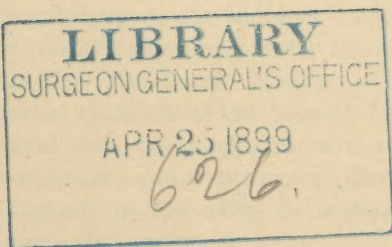
GUSTAV FÜTTERER, M.D.



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CONTRIBUTIONS TO THE HISTOLOGY, PHYSIOLOGY AND PATHOLOGY OF THE LIVER, BILE PASSAGES, AND BILE.

(*Third Paper.*)

BY GUSTAV FÜTTERER, M.D., CHICAGO,

Professor of Medicine, Chicago Policlinic; Fellow of the Chicago Academy of Medicine, etc.

THE ELIMINATION OF BACTERIA FROM THE GENERAL CIRCULATION BY THE LIVER AND THROUGH THE BILE PASSAGES.

Having observed in a number of post-mortem examinations of kidneys but few miliary tubercles, as compared with their number in other organs, I concluded that tubercle bacilli can pass through the normal kidneys without causing characteristic changes in the tissues. This is the only conclusion to which such findings can lead, as there is no reason to suppose that a smaller number of tubercle bacilli reached the kidneys than other organs. They must, therefore, have been eliminated by the kidneys. Considering such an elimination a very important factor in general infections, and believing that it also takes place through other organs, I was surprised by the appearance of a paper by Wyssokowitsch¹ in which he asserts that bacteria which have entered the circulation can be found in urine only when there are pathological changes in the kidneys. Considering my findings in reference to the kidneys as quite convincing, I entered upon a line of experiments which proved the same with reference to the liver, at the same time suggesting to Dr. Friedrich Schwyzer,² of Zürich, to investigate by experimental work this question in reference to the kidneys. Dr. Schwyzer published the results of his investigations under the title "Ueber das Durchgehen von Bacillen Durch die Nieren." He found color granules in the contorted channels of the kidneys half an hour after they had been injected into the blood-current, and he thinks it probable that micro-organisms can pass through the normal kidneys, but says that they appear in the urine in masses only after the glomeruli have become partly affected.

Since Schwyzer's experiments were made Posner and Lewin³ injected cultures of bacillus prodigiosus into the intestines, finding them again in the bile, the blood contained in the heart, the scrapings of kidney substance, and in the urine. They say: "It seems that bacteria coming from the intestinal canal in their passage through the urinary tract are excreted, without causing any lesions, if normal conditions exist. If those organs are changed pathologically, or if there is a retention of secretions, congestion, or disorder

of nutrition which predispose; then bacteria may accumulate and cause purulent inflammation.” *

Biedel and Kraus⁴ found micro-organisms which had been injected into the blood-current, such as staphylococcus aureus, bacterium coli and anthrax, in the urine (which was free from albumen and blood) a few minutes after the injection had been made, and they came to the conclusion that the micro-organisms had been excreted by normal kidneys.

In July, 1898, I reported in MEDICINE⁵ the successful cultivation of the bacillus prodigiosus, from the pelvis of the kidney, two minutes after their injection into the jugular vein of a dog. *These experiments prove that micro-organisms can pass through the normal kidneys, from the blood-current to the urinary passages, in a few minutes.*

To study the question of elimination of bacteria from the blood by the liver, I selected the bacillus pyocyaneus, resected a part of two costal cartilages near the left sternal margin, opened the pericardial cavity, and injected some of the culture mixed with normal salt solution into the left ventricle of the heart. I killed the animals experimented upon at different times after the injection had been made, and then after opening the gall-bladder in the most careful way, cultured pyocyaneus from the bile an hour and a half after the injection was made. As early as 1888 I found and cultivated the typhoid bacillus in the bile of two individuals who had died of typhoid fever. This observation was published under the joint authorship of Anton⁶ and myself, I contributing the anatomical and bacteriological part, and was the first recorded observation. Finding them in pure culture, I concluded that they came by way of the blood-current, and not direct from the intestinal canal. The typhoid bacillus has since been found by a great number of observers, but only a few have studied the process of elimination through the liver.

Trambusti and Maffuci⁷ infected rabbits and guinea-pigs with anthrax and bacillus typhi, afterwards finding both in the bile. They believed that the typhoid bacilli had passed through the liver without changes of this organ having taken place. The anthrax, which they only found once in the bile, they think cannot pass through the liver without causing tissue lesions.

Blachstein⁸ injected cultures of bacterium coli commune into the ear vein of rabbits, and cultured the bacterium from the bile as early as seven hours, and as late as thirty-eight days, after injection. He also experimented with the bacillus typhi abdominalis, culturing

it from the bile as early as ten days, and as late as fifteen and a half weeks. Blachstein's experiments were not made with the view of learning how soon bacteria appear in the bile.

Corrado⁹ says: "If we consider our own results and the results of others, it has been well stated that certain bacteria, if they are found in the blood in great masses, can be eliminated with the bile without our being able to find changes of the liver or bile passages, while greater masses can only get into the bile under pathologic conditions." Corrado considers the elimination of bacteria in infectious diseases as a symptom and not as a proof of a protective process.

Pernice and Scagliosi¹⁰ injected anthrax hypodermically in guinea-pigs and found it in the bile after from four to sixty-six hours. After injecting bacillus pyocyaneus hypodermically into eight guinea-pigs and killing them at different lengths of time, the results were: After one, two and four hours, negative; after six, twelve, twenty-two and seventy-two hours, positive; after five days, positive. They injected the bacillus subtilis hypodermically, and after six hours found it in the bile. Their examinations were made immediately after the death of the animals. They found that after injection of pure cultures, the staphylococcus pyogenes aureus, the bacillus pyocyaneus, the bacillus subtilis and the micrococcus prodigiosus are eliminated in many different ways. The elimination commences in from four to six hours after they have become distributed through the circulation, and it lasts when they have been injected with pathogenic micro-organisms until the death of the animal. The elimination commences in from twenty-four to forty-eight hours later, when non-pathogenic organisms are injected.

In 1893 Sherrington¹¹ injected bacteria intravenously and hypodermically and came to the conclusion that they are only eliminated after lesions of the tissues have taken place.

The investigations of Biedel and Kraus¹² are very instructive. In their first series of experiments, after injecting staphylococcus aureus intravenously, they cultured the bacteria from the gall-bladder. In the second series the bile was obtained through a glass cannula inserted into the common duct, the cystic duct having been ligated.

First Series.—Experiment No. 1, from gall-bladder, after 2 hours, negative; experiment No. 2, from gall-bladder, after 1 hour 40 minutes, positive; experiment No. 3, from gall-bladder, after 2½ hours, positive; experiment No. 4, from gall-bladder, after 2 hours, negative.

Second Series.—Experiment No. 1, from duct. chol., after 13 minutes, positive; experiment No. 2, from duct. chol., after 20 minutes, positive; experiment No. 3, from duct. chol., after 35 minutes, positive.

They also state that the elimination of staphylococcus aureus was an almost continual one for one and a half to two hours, while the experiment was carried on. If they had used large quantities of bile for inoculation they would have found the germs sooner. Their experiments show quite a difference as to results, according to the method employed, and I have therefore adopted their newer method, with good results.

F. J. Cotton¹⁴ experimented on rabbits, using bacillus anthracis, subtilis, prodigiosus, bacillus pneumoniae, staphylococcus aureus, and diplococcus pneumoniae. He injected the bacteria into the posterior ear vein; killed the animals after different lengths of time, and then took bile from the gall-bladder with all due care. The anthrax was not found in the bile by culture, but he only discovered a thread of anthrax in a bile-duct of a microscopic section, although he allowed thirty-six hours to elapse after injection. Cotton also had negative results after injecting bacillus subtilis, even after waiting for seven and a half hours. Of the pneumococcus, he found great masses two days after injection. The liver cells in those cases showed at the most a questionable parenchymatous degeneration. The small bile-ducts appeared normal, while the larger ones showed a well developed desquamative process. The endothelia of the blood-vessels were normal. The injection of staphylococcus aureus gave a positive result after ten minutes, while histologically only an indication of gathering leucocytes could be stated in the otherwise normal liver. His results with the staphylococcus were as follows:

Findings in the bile after 20 minutes, negative; 20 minutes, negative; 30 minutes, positive; 1½ hours, positive; 2½ hours, positive; 3½ hours, positive; 3½ hours, negative; 5 hours, negative; 5½ hours, positive; 6 hours, positive; 6 hours, positive; 7½ hours, negative; 17 hours, negative; 18 hours, negative; 20 hours, positive; 20½ hours, negative; 23 hours, positive; 23 hours, negative; 24 hours, negative; 27 hours, negative; 28 hours, large masses; 40 hours, large masses; 40 hours, positive; 44 hours, positive; 6 days, large masses; 8½ days, negative.

Bacillus Prodigiosus.—Findings in the bile after 30 minutes, positive; 4 hours 20 minutes, negative; 18 hours, negative; 20½ hours, negative; 24 (?) hours, negative.

Bacillus Pneumoniæ.—Findings in the bile after 2½ hours, negative; 3 hours, negative; 4½ hours, positive; 6¾ hours, positive; 20 hours, positive.

Such irregular findings would surely indicate that the method employed (culturing from the gall-bladder) is at fault.

I have referred to some writings on elimination of bacteria through the kidneys, as they have a bearing on the same function of the liver. It seems to me impossible to prove by microscopic examination the absence of histological lesions which allow micro-organisms to pass through the organ into its secretions. As the whole organ cannot be accurately examined, there may be an opening somewhere that escapes detection. Even in well-examined microscopic specimens there may be openings in the intercellular connections which are not recognized. As positive findings are of value, microscopic examination of the organs in such work should not be discouraged, but negative results are of no value. The examination of the urine for albumen and blood as practised by Biedel and Kraus is more important. I believe that the appearance of micro-organisms in the urine after having been injected into the blood-current, not associated with albumen and blood, proves that they are eliminated by normal kidneys. We have no similarly accurate test to apply to the secretions of the liver, but as micro-organisms pass this organ with even greater rapidity we may partly by analogy reach the same conclusions. We need not rely on this analogy altogether, as the elimination of bacteria from the liver becomes perfect when they get into the lumina of the small bile-ducts. I shall devote another chapter to the microscopical findings; thus the irregular flow of bile which has had such influence on our findings so far will become less important.

In a former paper (MEDICINE, July, 1898) I reported that bacteria injected into the portal vein had been cultured from the blood of the jugular veins within a minute's time, and now I can state that bacteria (*staphylococcus aureus* and *bacillus prodigiosus*) after being injected into a jugular vein were cultured from the common duct within two and three minutes in large masses. The experiments lasted half an hour, specimens of bile being taken before injection, to show that the bile was sterile, then every minute for five minutes, and thereafter every five minutes. The masses increased steadily, so that I am now fully convinced that the normal liver excretes large masses of micro-organisms. It appears that there is a difference in time for the appearance of the different germs, *bacillus anthracis* appearing particularly late, and probably

only after causing histological lesions. With the bacillus tuberculosis, which to my knowledge has not been employed by other investigators, and only in an unsatisfactory way by myself, as mentioned in my last paper (MEDICINE, July, 1898), I shall at an early date repeat the experiments. It seems to me that the great differences now existing as to time will be materially reduced if the experiments are carried on under more favorable and like conditions. The dog seems to be the proper animal to experiment with, as the common duct of a large dog will allow the introduction of a cannula of sufficient size. A small cannula does not allow the bile to pass through freely. I even do not rely on the small quantity of bile coming through a larger cannula, but introduce the needle of the syringe deep into the cannula in order to draw from one-half to a whole syringeful of bile for inoculation.

If we intend to state how early the micro-organisms appear in the bile, this is certainly a better way to proceed than to examine the contents of the gall-bladder. It is also better to feed the dog an hour or two before the experiment is begun. It must not be forgotten that by opening the abdomen we remove one of the main factors which promote elimination of bile from the liver—I mean the pressure of the diaphragm, and the pressure of the muscular walls of the abdomen. The diaphragmatic pressure can exert its full influence on the liver only when there is sufficient counter-pressure from the abdominal walls; therefore, a general pressure exercised over the part of the thorax covering the liver, like in performing artificial respiration, becomes quite necessary and will increase the flow of bile. Like Biedel and Kraus, I considered it of the utmost importance to state how early an elimination of bacteria begins, as an early elimination indicates a physiological process, and as the germs found also appeared in greater masses, *I do not hesitate to state that the normal liver eliminates great masses of bacteria from the blood-current within a few minutes after infection, and that this organ therefore acts as a protector in the sense of Cohnheim.* But the elimination will sometimes be incomplete, and as a consequence a number of different pathological conditions can arise. Pathogenic micro-organisms on their way through the liver may cause pathological changes of the bile passages, and of the intestinal channel, from where they may again invade the general circulation by way of the lymphatics, or by the portal vein, thus again reaching the liver. Tubercle bacilli may cause a tubercular enteritis, and typhoid bacilli relapses of typhoid fever. As there is such a general typhoid infection without intestinal lesions (Chiari and Kraus¹⁵), the elimi-

nation of typhoid bacilli in such cases may cause *secondarily* the characteristic anatomical lesions of the intestines. All these possibilities are of very great clinical importance, as is also the presence of typhoid bacilli in the gall-bladder in relation to the formation of gall-stones.

While the kidneys and liver, according to the great amount of bile and urine excreted during twenty-four hours, eliminate the largest amount of micro-organisms, other organs—the lungs, the mucous membranes of the respiratory tract, the intestinal and the urinary tract—as also the skin, participate in this function, and clinically we should do all in our power to stimulate such physiological action. In reference to the liver a better knowledge of the action of the different cholagogues than is at present obtainable would assist us materially, while now we should rely more on well regulated massage of the region of the liver, proper exercise, and feeding. The employment of proper antiparasitic remedies, some of which are excreted mainly by the liver, like the salicylates, which also act as cholagogues (Stadelmann¹⁷), would be indicated.

It seems hardly necessary to remark that if the liver is flooded with large masses of bacteria, or several infections occur at short intervals, this may partly close the filter by filling up the capillaries, and that obstructions of the bile passages or histological lesions in the liver will interfere with the process of elimination.

In answer to Cotton, who states that I have not suggested any theory in connection with the results of my first experiments, I would cite the exact words in my paper of 1888, literally translated: "In the past often repeated experiments have proven to me that micro-organisms may pass through the liver easily." And also, page 13: "The bile does not seem to have any antiparasitic action which is of any account, and an elimination of micro-organisms through the liver and with the bile is certainly not (I might have said not always) to be considered as a real elimination from the body, but pathogenic germs will, under favorable conditions, be able again to exercise their pathogenic properties in the intestinal canal." That means that there may be a complete or an incomplete elimination, the latter passage naturally including my intention to indicate that relapses of typhoid fever may occur in this way. In the latter respect I would also refer to another one of my papers ("The Liver as an Organ of Elimination of Corpuscular Elements," *MEDICINE*, August, 1895).

It is true that while writing my first paper I believed in an elimination through normal organs, but I could not—at that time—and

did not state that those micro-organisms had been excreted by the normal liver. Other theories than those mentioned could, as far as I am aware, not have been advanced, and have not been advanced since.

I also wish to correct an erroneous opinion of Biedel and Kraus,¹³ who say: "His (meaning Fütterer), as also the investigations of Pernice and Scagliosi, refer to results which were obtained from the gall-bladder after the animals had succumbed to the infection." I cannot see how such conclusions can be drawn from what I said, and will cite my own words:⁶ "In the past repeated experiments have proven to me that micro-organisms may pass through the liver easily. To gain some information on this question, I have used bacillus pyocyaneus, a germ well adapted for such experiments, as it can easily be recognized. After resecting several costal cartilages at the left sternal margin, and opening the pericardial sac, I injected bacillus pyocyaneus in pure culture, mixed with a sterilized physiological salt solution, into the left ventricle of the heart, and have always succeeded in culturing the germs from the bile when at least one and a half hours had elapsed after the injection had been made." It cannot be presumed that the infection with bacillus pyocyaneus killed those animals within the few hours used for the experiment. I proceeded exactly as Biedel and Kraus and other investigators did, namely, I killed the animals at different times after the germs had been injected; then I took samples of the bile from the gall-bladder, and used all necessary precautions.

I wish to correct an error which occurred in my paper in MEDICINE for August, 1895, that reads, "I then commenced experimenting with animals," while it should have read, "I then *again* commenced experimenting, etc.," as my first experiments were made long before I stated the presence of typhoid bacilli in the bile of human gall-bladders, as reported in my first paper in 1888.

It gives me great pleasure to render my sincere thanks to Dr. Emil Ries and to Dr. Leo Loeb, who have kindly assisted me in my experimental work.

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(Fourth Paper.)

A CLAIM FOR PRIORITY IN STATING THE PRESENCE OF THE BACILLUS TYPHI ABDOMINALIS IN THE GALL-BLADDER.

Over ten years have elapsed since I discovered the presence of the typhoid bacilli in the gall-bladders of two individuals who had died of typhoid fever. My observations were published in the *Münchener Medicinische Wochenschrift*, No. 19, 1888, under the title "Untersuchungen ueber Typhus Abdominalis." The paper was published under the joint authorship of Dr. B. Anton and Dr. G. Fütterer. Since the publication of this paper, the fact that I was the first to call attention to the presence of the typhoid bacilli in the gall-bladder has been largely overlooked by medical writers.

The paper in question is divided into two parts. The first, having been written by Dr. B. Anton, deals with a case of parotitis, giving the clinical description of the case and the ante-mortem conditions. The second or anatomico-bacteriological part gives the post-mortem findings in the above mentioned case of parotitis, and describes the post-mortem examination of two typhoid fever cases. It was in the last two cases that a bacteriological examination of bile in the gall-bladder revealed the presence of typhoid

bacilli. The second part of the paper is published in my name only, and is, I believe, the first statement of this kind to be found in medical literature.

IN VIEW OF THESE FACTS I FEEL THAT I MAY JUSTLY CLAIM TO HAVE BEEN THE FIRST TO DISCOVER THE PRESENCE OF THE TYPHOID BACILLI IN THE GALL-BLADDER. I ALSO CLAIM PRIORITY FOR EXPRESSING THE OPINION THAT THE RELAPSES OF TYPHOID FEVER ARE CAUSED BY TYPHOID BACILLI ENTERING THE INTESTINES WITH THE BILE, A CONCLUSION EASILY REACHED FROM THESE FINDINGS.

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